Clinical trial results:
Proof of Mechanism Study to Assess the Potential of GSK239512 to Remyelinate Lesions in Subjects with Relapsing Remitting Multiple Sclerosis.

Summary

EudraCT number	2012-003627-38
Trial protocol	SE DE ES CZ BG GB
Global end of trial date	12 September 2014

Results information

Result version number	v2 (current)
This version publication date	26 March 2016
First version publication date	29 April 2015
Version creation reason	• Correction of full data set Minor corrections required.

Trial information

Trial identification

Sponsor protocol code	H3M116477

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 October 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 September 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Estimation of the effects of GSK239512 on lesion remyelination in subjects with Relapsing Remitting Multiple Sclerosis on stable treatment
with Avonex [interferon-beta1a] or Copaxone [glatiramer acetate].

Protection of trial subjects:

A 4-week flexible titration period was used to achieve the final dose for each participant to minimize the occurrence of adverse events. In addition, participants were permitted to down-titrate during the maintenance period, if they experienced tolerability issues.

This study did not require participants to return to the study site for evaluation of relapses, if they chose to go to their local physician. This study did not restrict the use of rescue medications (e.g. glucocorticoids) to manage the occurrence of a relapse. However, due to the potential interference with the magnetic resonance imaging (MRI), , if a relapse requiring management with glucocorticoids occurred around the time of a scheduled MRI, the MRI was to be rescheduled to ensure that the subject has a minimum of a 1 week washout period following completion of treatment with glucocorticoids.

The study included flexible visit day scheduling to allow inclusion of holiday periods over the 1 year duration with intensive visit schedule.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	01 February 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Bulgaria: 12
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Ukraine: 51
Worldwide total number of subjects	131
EEA total number of subjects	75

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	131
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants (par.) diagnosed with a relapsing-remitting multiple sclerosis (RRMS) on stable background treatment with either avonex or copaxone were eligible to participate.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo QD

Arm description:

Participants received GSK239512 matching placebo tablets orally once daily (QD) during the 4 week titration period followed by the 44 week treatment maintenance period. The treatment period could be adapted to a 5 week titration and 43 week maintenance period, if needed. A single down-titration was allowed during the maintenance period if MTD was lower than the maximum dose achieved during titration. Participants continued with their current standard of care background disease modifying therapy (DMT) of either avonex or copaxone throughout the study.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo - 10 µg, 20 µg, 40 µg, or 80 µg once daily

Arm title	GSK239512 QD

Arm description:

Participants received titration doses of GSK239512 tablets orally QD, starting at 10 micrograms (µg) and increased up to 80 µg during the 4 week titration period (10 µg first week, 20 µg second week, 40 µg third week, 80 µg fourth week) in order to select the maximum tolerated dose (MTD). Participants continued on the MTD of GSK239512 during the 44 week treatment maintenance period. The treatment period could be adapted to a 5 week titration and 43 week maintenance period, if needed. A single down-titration was allowed during the maintenance period if MTD was lower than the maximum dose achieved during titration. Participants continued with their current standard of care background DMT of either avonex or copaxone throughout the study.

Arm type	Experimental
Investigational medicinal product name	GSK239512
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 µg, 20 µg, 40 µg, or 80 µg once daily

Number of subjects in period 1	Placebo QD	GSK239512 QD
Started	66	65
Completed Titration Phase	66	65
Completed	63	51
Not completed	3	14
Consent withdrawn by subject	2	5
Physician decision	-	2
Adverse event, non-fatal	-	7
Protocol-defined Stopping Criteria	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Placebo QD

Reporting group description:

Participants received GSK239512 matching placebo tablets orally once daily (QD) during the 4 week titration period followed by the 44 week treatment maintenance period. The treatment period could be adapted to a 5 week titration and 43 week maintenance period, if needed. A single down-titration was allowed during the maintenance period if MTD was lower than the maximum dose achieved during titration. Participants continued with their current standard of care background disease modifying therapy (DMT) of either avonex or copaxone throughout the study.

Reporting group title	GSK239512 QD

Reporting group description:

Participants received titration doses of GSK239512 tablets orally QD, starting at 10 micrograms (µg) and increased up to 80 µg during the 4 week titration period (10 µg first week, 20 µg second week, 40 µg third week, 80 µg fourth week) in order to select the maximum tolerated dose (MTD). Participants continued on the MTD of GSK239512 during the 44 week treatment maintenance period. The treatment period could be adapted to a 5 week titration and 43 week maintenance period, if needed. A single down-titration was allowed during the maintenance period if MTD was lower than the maximum dose achieved during titration. Participants continued with their current standard of care background DMT of either avonex or copaxone throughout the study.

Reporting group values	Placebo QD	GSK239512 QD	Total
Number of subjects	66	65	131
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	36.2	36.4	
standard deviation	± 7.82	± 7.95	-
Gender categorical			
Units: Subjects			
Female	41	42	83
Male	25	23	48
Race			
Units: Subjects			
White - Arabic/North African Heritage	0	1	1
White - White/Caucasian/European Heritage	66	64	130
Expanded Disability Status Scale			
Numerical Scale from 1-10 assessing Disability status of participants with Multiple Sclerosis			
Units: Subjects			
1.0	6	4	10
1.5	18	14	32
2.0	7	12	19
2.5	11	11	22
3.0	5	11	16
3.5	11	5	16
4.0	4	4	8
4.5	4	4	8

End points

End points reporting groups

Reporting group title	Placebo QD

Reporting group description:

Participants received GSK239512 matching placebo tablets orally once daily (QD) during the 4 week titration period followed by the 44 week treatment maintenance period. The treatment period could be adapted to a 5 week titration and 43 week maintenance period, if needed. A single down-titration was allowed during the maintenance period if MTD was lower than the maximum dose achieved during titration. Participants continued with their current standard of care background disease modifying therapy (DMT) of either avonex or copaxone throughout the study.

Reporting group title	GSK239512 QD

Reporting group description:

Participants received titration doses of GSK239512 tablets orally QD, starting at 10 micrograms (µg) and increased up to 80 µg during the 4 week titration period (10 µg first week, 20 µg second week, 40 µg third week, 80 µg fourth week) in order to select the maximum tolerated dose (MTD). Participants continued on the MTD of GSK239512 during the 44 week treatment maintenance period. The treatment period could be adapted to a 5 week titration and 43 week maintenance period, if needed. A single down-titration was allowed during the maintenance period if MTD was lower than the maximum dose achieved during titration. Participants continued with their current standard of care background DMT of either avonex or copaxone throughout the study.

Primary: Mean change in gadolinium enhanced (GdE) lesion magnetization transfer ratio (MTR) value post-Lesion (PoL) from pre-Lesion (PrL)

End point title	Mean change in gadolinium enhanced (GdE) lesion magnetization transfer ratio (MTR) value post-Lesion (PoL) from pre-Lesion (PrL)

End point description:

Brain magnetic resonance imaging (MRI) scans were performed to assess MTR values for gadolinium GdE lesions. GdE lesions are areas of inflammation detected by injecting GdE. Changes in MTR values are indicative of changes in brain myelin content associated with lesion remyelination. MRI scans were performed at Baseline, Weeks 6, 12, 18, 24, 30, 36, 42 and 48. The change in MTR value PoL from PrL was the change in the average PoL MRI scans MTR from the average PrL MRI scans MTR. The analysis method used was the mixed-model repeated measures (MMRM) adjusted for treatment, relative MRI, lesion volume, background MS DMT, average PrL MTR, and treatment, lesion volume, background DMT and average PrL MTR all by relative MRI. Analysis excluded MRI scans within 70 days of lesion occurrence and included data for lesions with at least 2 MRI assessments PrL and PoL. Intent-to-Treat (ITT) Population: par. who received >=1 dose of investigational product post randomization.

End point type	Primary

End point timeframe:

Up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	28[1]	27[2]		
Units: MTR				
least squares mean (standard error)	-0.689 (± 0.0579)	-0.541 (± 0.0643)		

Notes:

[1] - ITT Population. Par. with evaluable lesions available at the specified time points were analyzed.

[2] - ITT Population. Par. with evaluable lesions available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	superiority[3]
Method	Mixed models analysis
Parameter estimate	Effect Size
Point estimate	0.344
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.018
upper limit	0.671

Notes:

[3] - The standardized Effect Sizes were derived as the treatment difference divided by the standard deviation (estimated as the between subject variability from the analysis model) of the treatment difference averaged across visits 'Relative MRIs'". Posterior Probability that Effect Size is >0 is 0.955

Primary: Mean change in Delta-MTR Lesions MTR value PoL from PrL

End point title	Mean change in Delta-MTR Lesions MTR value PoL from PrL

End point description:

Brain magnetic resonance imaging (MRI) scans were performed to assess MTR of Delta-MTR lesions. Delta-MTR lesions are areas of change in MTR detected by comparison to prior images. Changes in MTR values are indicative of changes in brain myelin content associated with lesion remyelination. MRI scans were performed at Baseline, Weeks 6, 12, 18, 24, 30, 36, 42 and 48. The change in MTR value PoL from PrL was the change in average PoL MRI scans MTR from the average PrL MRI scans MTR. The analysis method was MMRM adjusted for treatment, relative MRI, lesion volume, background MS DMT, average PrL MTR, treatment by relative MRI, lesion volume by relative MRI, background DMT by relative MRI and average PrL MTR by relative MRI. Analysis excluded MRI scans within 70 days of lesion occurrence and included data for lesions with at least 2 MRI assessments PrL and PoL.

End point type	Primary

End point timeframe:

Up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29[4]	24[5]		
Units: MTR				
least squares mean (standard error)	-0.769 (± 0.0597)	-0.665 (± 0.0725)		

Notes:

[4] - ITT Population. Par. with evaluable lesions available at the specified time points were analyzed.

[5] - ITT Population. Par. with evaluable lesions available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v GSK239512 QD

Number of subjects included in analysis	53
Analysis specification	Pre-specified
Analysis type	superiority[6]
Method	Mixed models analysis
Parameter estimate	Effect Size
Point estimate	0.243
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.112
upper limit	0.598

Notes:

[6] - The standardized Effect Sizes were derived as the treatment difference divided by the standard deviation (estimated as the between subject variability from the analysis model) of the treatment difference averaged across visits 'Relative MRIs'". Posterior Probability that Effect Size is >0 is 0.877

Secondary: Change from Baseline in T2 lesion MTR at Week 48

End point title	Change from Baseline in T2 lesion MTR at Week 48

End point description:

Brain MRI scans were performed to assess MTR of T2 lesions, which is indicative of brain myelin content. Changes in MTR values are indicative of changes in brain myelin content associated with lesion remyelination. T2 lesions are also called hyperintense lesions, meaning that they appear as bright spots on the MRI image. Baseline was defined as the participant's last available assessment prior to initiation of study medication. Change from Baseline was calculated as the Week 48 value minus the Baseline value. The analysis method was MMRM adjusted for treatment, visit, screening T2 lesion MTR value, background MS DMT, treatment by visit, screening T2 lesion MTR value by visit and background DMT by visit.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57[7]	50[8]		
Units: MTR				
least squares mean (standard error)	0.002 (± 0.0128)	-0.02 (± 0.0134)		

Notes:

[7] - ITT Population. Par. with evaluable lesions available at the specified time points were analyzed.

[8] - ITT Population. Par. with evaluable lesions available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	107
Analysis specification	Pre-specified
Analysis type	superiority[9]
Method	Mixed models analysis
Parameter estimate	Effect Size
Point estimate	-0.246

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.588
upper limit	0.095

Notes:

[9] - The standardized Effect Sizes were derived as the treatment difference divided by the standard deviation (estimated as the between subject variability from the analysis model) of the treatment difference averaged across visits 'Relative MRIs'".

Secondary: Cumulative number of new GdE lesions, new enlarging T2 lesions and combined unique active lesions at Week 48

End point title	Cumulative number of new GdE lesions, new enlarging T2 lesions and combined unique active lesions at Week 48

End point description:

The cumulative number of new GdE lesions (NGL), new enlarging T2 lesions (NET2L) and cumulative unique active lesions (CUAL) per scan at Week 48 were analyzed. The analysis was performed by general linear model assuming an underlying negative binomial distribution with a log-link function adjusted for treatment, background DMT and gadolinium enhancing lesion screening status to evaluate the mean number of lesions per MRI scan. The all evaluable scans dataset was used which included all evaluable on-treatment MRI scans for each participant.

End point type	Secondary

End point timeframe:

Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[10]	64[11]		
Units: Mean rates of lesions per MRI scan				
number (not applicable)				
NGL	0.66	1.14		
NET2L	1.45	1.71		
CUAL	1.48	1.74		

Notes:

[10] - ITT Population. Par. with post-Baseline MRI were analyzed.

[11] - ITT Population. Par. with post-Baseline MRI were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[12]
Method	General Linear Model
Parameter estimate	Ratio
Point estimate	1.72

Confidence interval	
level	90 %
sides	2-sided
lower limit	1.05
upper limit	2.82

Notes:

[12] - Treatment Comparison ratio for NGL at Week 48.

Statistical analysis title	Analysis 2
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[13]
Method	General Linear Model
Parameter estimate	Ratio
Point estimate	1.18
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.75
upper limit	1.85

Notes:

[13] - Treatment Comparison ratio for NET2L at Week 48.

Statistical analysis title	Analysis 3
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[14]
Method	General Linear Model
Parameter estimate	Ratio
Point estimate	1.17
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.74
upper limit	1.85

Notes:

[14] - Treatment Comparison ratio for CUAL at Week 48.

Secondary: Change from Baseline in whole brain volume at Week 48

End point title	Change from Baseline in whole brain volume at Week 48

End point description:

Whole brain volume is a measure of brain size determined by a MRI scan. Baseline is defined as the participant's last available assessment prior to initiation of study medication. The normalized brain volume at Week 48 was derived from the dataset presenting change from baseline as follows: Week 48 Volume = Baseline Volume plus (Baseline Volume x Relative Change at Week 48). The analysis was performed by the analysis of covariance adjusted for treatment, screening brain volume, and background MS DMT. The observed case (OC) dataset was used which contained all the available change from Baseline responses for each participant without missing values being estimated or data carried forward.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59[15]	50[16]		
Units: Centimeter cube				
least squares mean (standard error)	-3.6 (± 0.81)	-4.6 (± 0.89)		

Notes:

[15] - ITT Population. Only those par. available at the specified time points were analyzed.

[16] - ITT Population. Only those par. available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	GSK239512 QD v Placebo QD
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority[17]
Method	ANCOVA
Parameter estimate	Effect Size
Point estimate	-0.2
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.5
upper limit	0.2

Notes:

[17] - Placebo QD versus GSK239512 QD for whole brain volume at Week 48. Effect size is the difference of the means in the two treatment groups divided by the standard deviation from the statistical model.

Secondary: Change from Baseline in white matter volume and grey matter volume at Week 48

End point title	Change from Baseline in white matter volume and grey matter volume at Week 48

End point description:

White matter volume and grey matter volume are measures of size of different areas of the brain determined by a MRI scan. Baseline is defined as the participant’s last available assessment prior to initiation of study medication. The white matter volume and grey matter volume at a post Baseline MRI was derived as follows: Post Baseline Volume = Baseline Volume plus (Baseline Volume x Relative Change Post Baseline). Change from Baseline in each volume was calculated as the Week 48 value minus the Baseline value. The analysis was performed using a mixed model for repeated measures adjusted for treatment, visit, baseline volume, background MS DMT, interactions between visit are also included. The observed case (OC) dataset was used which contained all the available change from Baseline responses for each participant at each visit, without missing values being estimated or data carried forward.

End point type	Secondary

End point timeframe:

Baseline and Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59[18]	50[19]		
Units: Centimeter cube				
least squares mean (standard error)				
White matter volume	1.2 (± 0.55)	0.2 (± 0.59)		
Grey matter volume	-4.1 (± 0.52)	-4.4 (± 0.55)		

Notes:

[18] - ITT Population. Only those par. available at the specified time points were analyzed.

[19] - ITT Population. Only those par. available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority[20]
Method	Mixed models analysis
Parameter estimate	Effect Size
Point estimate	-0.3
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.6
upper limit	0.1

Notes:

[20] - Placebo QD versus GSK239512 QD for white matter volume at Week 48. Effect size is the difference of the means in the two treatment groups divided by the standard deviation from the statistical model.

Statistical analysis title	Analysis 2
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	superiority[21]
Method	Mixed models analysis
Parameter estimate	Effect Size
Point estimate	-0.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.5
upper limit	0.3

Notes:

[21] - Placebo QD versus GSK239512 QD for grey matter volume at Week 48. Effect size is the difference of the means in the two treatment groups divided by the standard deviation from the statistical model.

Secondary: Cumulative number of new unenhancing T1 lesions at Week 48

End point title	Cumulative number of new unenhancing T1 lesions at Week 48

End point description:

The cumulative number of new GdE lesions evolving into black holes (NGLEB) by Week 48 were analyzed. The analysis was performed by the general linear model assuming an underlying negative binomial distribution with a log-link function adjusted for treatment, background DMT and gadolinium enhancing lesion screening status. The all evaluable scans dataset was used which included all evaluable on-treatment MRI scans for each participant.

End point type	Secondary

End point timeframe:

Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[22]	64[23]		
Units: Number of lesions per scan				
number (not applicable)	0.5	0.69		

Notes:

[22] - ITT Population. Par. with post-Baseline MRI were analyzed.

[23] - ITT Population. Par. with post-Baseline MRI were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	superiority[24]
Method	General Linear Model
Parameter estimate	Ratio
Point estimate	1.38
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.87
upper limit	2.18

Notes:

[24] - Treatment Comparison ratio for UT1L at Week 48.

Secondary: Cumulative number of new GdE lesions evolving into black holes by Week 48

End point title	Cumulative number of new GdE lesions evolving into black holes by Week 48

End point description:

The cumulative number of new GdE lesions evolving into black holes (NGLEB) by Week 48 were analyzed. The analysis was performed by the general linear model assuming an underlying negative binomial distribution with a log-link function adjusted for treatment, background DMT and gadolinium enhancing lesion screening status. The all evaluable scans dataset was used which included all evaluable on-treatment MRI scans for each participant.

End point type	Secondary

End point timeframe:
Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63[25]	57[26]		
Units: Number of lesions per scan				
number (not applicable)	0.29	0.5		

Notes:
[25] - ITT Population. Only those par. available at the specified time points were analyzed.
[26] - ITT Population. Only those par. available at the specified time points were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[27]
Method	General Linear Model
Parameter estimate	Ratio
Point estimate	1.71
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.05
upper limit	2.78

Notes:
[27] - Treatment Comparison ratio for NGLEB at Week 48.

Secondary: Change from Baseline (BL) in CogState battery total score (TS), executive function composite score (EFCS), memory composite score (MCS) and attention composite score (ACS) at Week 48

End point title	Change from Baseline (BL) in CogState battery total score (TS), executive function composite score (EFCS), memory composite score (MCS) and attention composite score (ACS) at Week 48

End point description:

The CogState battery used in this study consists of 7 tasks for which multiple outcome measures are collected and used in the derivation of the composite cognitive domain scores. Test scores were interpreted on the basis of normative data and expected level of performance. The assessment was conducted at Screen (twice), BL, and Weeks 12, 24 and 48. Change from BL in TS, EFCS, MCS and ACS is summarised at Week 48.The BL is the mean of the second Screening assessment and the BL (pre-dose) assessment, if both were avail or the non-missing value if only one was avail. Change from BL is calculated as post-BL value minus BL value. The analysis method was MMRM adjusted for treatment, visit, BL executive function score, background MS DMT, and interaction by visit. Only those par. available at specified time points were analyzed. Different par. may have been analyzed at different time points, so the overall number of par. analyzed reflects everyone in the ITT Population.

End point type	Secondary

End point timeframe:
Baseline and Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[28]	65[29]		
Units: Score on a scale				
least squares mean (standard error)				
TS, n=56,48	0.16 (± 0.0482)	0.08 (± 0.0519)		
EFCS, n=55,47	0.079 (± 0.0651)	0.057 (± 0.0702)		
MCS, n=55,48	0.311 (± 0.0697)	0.157 (± 0.0745)		
ACS, n=54,47	-0.003 (± 0.0877)	-0.057 (± 0.0938)		

Notes:

[28] - ITT Population

[29] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority[30]
Method	Mixed models analysis
Parameter estimate	Effect Size
Point estimate	-0.237
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.588
upper limit	0.113

Notes:

[30] - Placebo QD versus GSK239512 QD for TS at Week 48. Effect size is the difference of the means in the two treatment groups divided by the standard deviation from the statistical model.

Statistical analysis title	Analysis 2
Comparison groups	GSK239512 QD v Placebo QD
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority[31]
Method	Mixed models analysis
Parameter estimate	Effect Size
Point estimate	-0.045
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.373
upper limit	0.283

Notes:

[31] - Placebo QD versus GSK239512 QD for EFCS at Week 48. Effect size is the difference of the means in the two treatment groups divided by the standard deviation from the statistical model.

Statistical analysis title	Analysis 3
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority[32]
Method	Mixed models analysis
Parameter estimate	Effect Size
Point estimate	-0.311
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.65
upper limit	0.028

Notes:

[32] - Placebo QD versus GSK239512 QD for MCS at Week 48. Effect size is the difference of the means in the two treatment groups divided by the standard deviation from the statistical model.

Statistical analysis title	Analysis 4
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority[33]
Method	Mixed models analysis
Parameter estimate	Effect Size
Point estimate	-0.092
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.447
upper limit	0.263

Notes:

[33] - Placebo QD versus GSK239512 QD for ACS at Week 48. Effect size is the difference of the means in the two treatment groups divided by the standard deviation from the statistical model.

Secondary: Relapse rate during the treatment phase

End point title	Relapse rate during the treatment phase

End point description:

A relapse is defined as participant-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the central nervous system (CNS). It must occur in the absence of fever or infection and should follow improvement from a previous relapse, occur at least 30 days following the onset of a previous relapse, and be persistent for at least 24 hours. The analysis method was a maximum likelihood based analysis, assuming the Negative Binomial distribution with time on treatment measured in days as an offset variable for relapse occurrence. The model included adjustment for background DMT and treatment.

End point type	Secondary

End point timeframe:

Up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[34]	65[35]		
Units: Rate of relapse				
number (not applicable)	0.4	0.417		

Notes:

[34] - ITT Population

[35] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority[36]
Method	Binomial Model
Parameter estimate	Ratio
Point estimate	1.044
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.615
upper limit	1.772

Notes:

[36] - Treatment Comparison Ratio for Relapse Rate

Secondary: Number of participants relapsing during the treatment phase

End point title	Number of participants relapsing during the treatment phase

End point description:

A relapse is defined as:"participant-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the central nervous system (CNS), current or historical". It must occur in the absence of fever or infection and should - follow improvement from a previous relapse, occur at least 30 days following the onset of a previous relapse, and be persistent for at least 24 hours. Number of participants relapsing during the treatment phase was analyzed using logistic regression adjusted for treatment and background DMT.

End point type	Secondary

End point timeframe:

Up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[37]	65[38]		
Units: Participants	20	18		

Notes:

[37] - ITT Population

[38] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority[39]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.47
upper limit	1.66

Notes:

[39] - Treatment Comparison Odds Ratio (GSK239512/Placebo). A ratio <1 indicates a lower risk with GSK239512 compared with placebo.

Secondary: Analysis of the time to first relapse

End point title	Analysis of the time to first relapse

End point description:

A relapse is defined as participant-reported symptoms or objectively observed signs typical of an acute inflammatory demyelinating event in the central nervous system (CNS). It must occur in the absence of fever or infection and should follow improvement from a previous relapse, occur at least 30 days following the onset of a previous relapse, and be persistent for at least 24 hours. Date of relapse was captured for each subject and occurrence, if a relapse occurred. Time tofirst relapse was calculated as the relapse onset date minus date study medication was started plus one day. Analysis was performed using using a Cox's Proportional Hazards model adjusting for background DMT. A hazard ratio <1 indicates a lower risk with GSK239512 compared with placebo.

End point type	Secondary

End point timeframe:

Up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[40]	65[41]		
Units: Number of participants relapsing	20	18		

Notes:

[40] - ITT Population

[41] - ITT Population

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	superiority[42]
Method	Cox's Proportional Hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.965
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.565
upper limit	1.647

Notes:

[42] - A hazard ratio <1 indicates a lower risk with GSK239512 compared with placebo.

Secondary: Expanded Disability Status Scale (EDSS) score at Week 48

End point title	Expanded Disability Status Scale (EDSS) score at Week 48

End point description:

EDSS is a scale to measure the disability status of participants with multiple sclerosis based on the presence of certain symptoms. EDSS provides a total score on a scale that ranges from 0 to 10 based on functional system (FS) scores and walking abilities. The first levels 1.0 to 4.5 refer to participants with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 are highly influenced by changes in walking ability. FS (with max score) are: visual converted (VC;4), brainstem (BS;5), pyramidal (P;6), cerebellar (Cr;5), sensory (S;6), bowel and bladder converted (BB;5), cerebral (Cb;5) and ambulatory (A; 12). Values are represented as mean values for the population at Baseline and Week 48.

End point type	Secondary

End point timeframe:

Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[43]	65[44]		
Units: EDSS score				
arithmetic mean (standard deviation)				
EDSS Total Score at Baseline, n=66, 65	2.45 (± 1.04)	2.48 (± 0.958)		
EDSS Total Score at Wk 48, n=57, 48	2.44 (± 1.126)	2.32 (± 1.049)		
VC Score at Baseline, n=66, 65	0.56 (± 0.747)	0.63 (± 0.741)		
VC Score at Wk 48, n=57, 48	0.61 (± 0.84)	0.69 (± 0.748)		
BS Score at Baseline, n=66, 65	0.76 (± 0.786)	0.78 (± 0.739)		
BS Score at Wk 48, n= 57, 48	0.65 (± 0.694)	0.79 (± 0.743)		
P Score at Baseline, n=66, 65	1.53 (± 1.056)	1.51 (± 0.986)		
P Score at Wk 48, n=57, 48	1.54 (± 1.036)	1.46 (± 0.922)		
Cr Score at Baseline, n=66, 65	1.05 (± 0.968)	1.05 (± 0.926)		
Cr Score at Wk 48, n=57, 48	0.96 (± 0.944)	0.98 (± 0.978)		
S Score at Baseline, n=66, 65	0.98 (± 0.813)	0.94 (± 0.966)		
S Score at Wk 48, n=57, 48	0.84 (± 0.819)	0.92 (± 0.986)		
BB Score at Baseline, n=66, 65	0.52 (± 0.707)	0.65 (± 0.779)		

BB Score at Wk 48, n=57, 48	0.44 (± 0.655)	0.54 (± 0.683)		
Cb Score at Baseline, n=66, 65	0.67 (± 0.73)	0.74 (± 0.796)		
Cb Score at Wk 48, n-57, 48	0.56 (± 0.708)	0.65 (± 0.785)		
A Score at Baseline, n=66, 65	0.64 (± 0.624)	0.55 (± 0.613)		
A Score at Wk 48, n=57, 48	0.65 (± 0.855)	0.52 (± 0.618)		

Notes:

[43] - ITT Population

[44] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with the indicated change from the BL in EDSS score over 48 weeks

End point title	Number of participants with the indicated change from the BL in EDSS score over 48 weeks

End point description:

EDSS is a scale to measure the disability status of par. with multiple sclerosis based on the presence of certain symptoms. EDSS provides a total score on a scale that ranges from 0 to 10 based on functional system (FS) scores and walking abilities. The first levels 1.0 to 4.5 refer to par.with high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 are highly influenced by changes in walking ability. Change from the Baseline in EDSS is summarised up to Week 48. Baseline is defined as the par's last available assessment prior to initiation of study medication. Improved is defined as a 1.0 decrease and worsened is defined as a 1.0 increase in EDSS score from baseline score. Only those par.available at the specified time points were analyzed (represented by n=X,X in category titles). Different par.may have been analyzed at different time points, so the overall number of par.analyzed reflects everyone in the ITT Population.

End point type	Secondary

End point timeframe:

Baseline and Week 12, 24, 36 and 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[45]	65[46]		
Units: Participants				
Week12, Improved, n=61,58	5	1		
Week12, Worsened, n=61,58	0	0		
Week24, Improved, n=60,56	4	3		
Week24, Worsened, n=60,56	1	2		
Week36, Improved, n=57,51	5	2		
Week36, Worsened, n=57,51	4	0		
Week48, Improved, n=57,48	5	3		
Week48, Worsened, n=57,48	4	1		

Notes:

[45] - ITT Population

[46] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with sustained worsening of the Expanded Disability Status Scale (EDSS) score at Week 48

End point title	Number of participants with sustained worsening of the Expanded Disability Status Scale (EDSS) score at Week 48

End point description:

EDSS is a scale to measure the disability status of participants with multiple sclerosis based on the presence of certain symptoms. EDSS provides a total score on a scale that ranges from 0 to 10 based on functional system (FS) scores and walking abilities. The first levels 1.0 to 4.5 refer to participants with a high degree of ambulatory ability and the subsequent levels 5.0 to 9.5 are highly influenced by changes in walking ability. FS are: pyramidal (P), cerebellar (Cr), brainstem (BS), sensory (S), bowel and bladder converted (BB), visual converted (VC), cerebral (Cb) and ambulatory (A). A sustained change is defined as a change that has been sustained for at least 12 weeks at Week 48. Participants that had worsened from BL by 2 or more points are included in the >=1 point and the >=2 points categories for that FS. BL is defined as the participants last available assessment prior to initiation of study medication.

End point type	Secondary

End point timeframe:

Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57[47]	48[48]		
Units: Participants				
VC Score Worsened by >=1 point	3	0		
VC Score Worsened by >=2 points	1	0		
BS Score Worsened by >=1 point	4	5		
BS Score Worsened by >=2 points	0	0		
P Score Worsened by >=1 point	7	4		
P Score Worsened by >=2 points	0	1		
Cr Score Worsened by >=1 point	1	3		
Cr Score Worsened by >=2 points	0	0		
S Score Worsened by >=1 point	2	3		
S Score Worsened by >=2 points	1	0		
BB Score Worsened by >=1 point	1	2		
BB Score Worsened by >=2 points	0	0		
Cb Score Worsened by >=1 point	4	2		
Cb Score Worsened by >=2 points	0	0		
A Score Worsened by >=1 point	4	0		
A Score Worsened by >=2 points	0	0		

Notes:

[47] - ITT Population

[48] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline at Week 48 in MSQoL Physical Function and Mental Function Composite Score

End point title	Change from Baseline at Week 48 in MSQoL Physical Function and Mental Function Composite Score

End point description:

MSQoL is a 54 item assessment of the quality of life status of patients with multiple sclerosis and the

Overall Quality of Life score is a composite of the physical function and mental function health composite scores. Scale scores were generated by averaging the items within scales and transforming the mean scores linearly from 0 to 100 possible scores, with higher scores indicating a better quality of life. BL is defined as the participants last available assessment prior to initiation of study medication. The assessment was conducted before randomized to treatment and at the end of treatment (Early Withdrawal or Week 48). The analysis was performed using an analysis of covariance adjusted for treatment, baseline composite score and background MS disease modifying therapy.

End point type	Secondary

End point timeframe:

Early Withdrawal, Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65[49]	63[50]		
Units: Scores on a scale				
arithmetic mean (standard error)				
Physical Function	1.98 (± 1.604)	-0.97 (± 1.622)		
Mental Function	2.13 (± 1.721)	-2.89 (± 1.744)		

Notes:

[49] - ITT Population. Only those par. with data available at the specified timepoints were analyzed.

[50] - ITT Population. Only those par. with data available at the specified timepoints were analyzed.

Statistical analyses

Statistical analysis title	Analysis 1
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[51]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-2.95
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6.72
upper limit	0.82

Notes:

[51] - Placebo QD vs GSK239512 QD for Physical Function. A comparison of the mean change from baselinesin each treatment group.

Statistical analysis title	Analysis 2
Comparison groups	Placebo QD v GSK239512 QD
Number of subjects included in analysis	128
Analysis specification	Pre-specified
Analysis type	superiority[52]
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	-5.02

Confidence interval	
level	90 %
sides	2-sided
lower limit	-9.06
upper limit	-0.98

Notes:

[52] - Placebo QD vs GSK239512 QD for Mental Function. A comparison of the mean change from baselines in each treatment group.

Secondary: Number of participants with any adverse events (AEs) and any serious adverse events (SAEs)

End point title	Number of participants with any adverse events (AEs) and any serious adverse events (SAEs)

End point description:

An AE is any untoward medical occurrence in a par. temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product. An SAE is any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, a congenital anomaly/birth defect, important medical events that jeopardize the par. or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. AEs and SAEs were assessed at Pre-TT phase (prior to first dose of investigational product (IP)), TT phase-48 Weeks (from first dose of IP to 3 days after last dose, including Titratration (T) and Maintenance (M) Periods) and Follow-Up phase (more than 3 days after last dose of IP)

End point type	Secondary

End point timeframe:

Up to Week 50

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[53]	65[54]		
Units: Participants				
Any AE, Pretreatment Phase	0	0		
Any AE, TT Phase	50	48		
Any AE, TT Phase, T Period	23	34		
Any AE, TT Phase, M Period	44	43		
Any AE, Follow-up Phase	5	6		
Any SAE, Pretreatment Phase	0	0		
Any SAE, TT Phase	2	3		
Any SAE, TT Phase, T Period	0	0		
Any SAE, TT Phase, M Period	2	3		
Any SAE, Follow-up Phase	0	0		

Notes:

[53] - ITT Population

[54] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of mild, moderate and severe AEs

End point title	Number of mild, moderate and severe AEs

End point description:

The Common Terminology Criteria for Adverse Events (CTCAE, Version 4) has categorised AEs in five grades. Grade refers to the severity of the AE. Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living. Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living. AEs and SAEs were assessed at Pre-TT phase (period prior to the first dose of investigational product (IP)), TT phase-48 Weeks (from first dose of IP to 3 days after last dose with Titration (T) and Maintenace (M) Periods) and Follow-Up phase (from more than 3 days after last dose of IP).

End point type	Secondary

End point timeframe:

Up to Week 50

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[55]	65[56]		
Units: Events				
Mild AE, Pretreatment Phase	0	0		
Moderate AE, Pretreatment Phase	0	0		
Severe AE, Pretreatment Phase	0	0		
Mild AE, TT Phase	138	157		
Moderate AE, TT Phase	62	85		
Severe AE, TT Phase	4	3		
Mild AE, TT Phase, T Period	34	64		
Moderate AE, TT Phase, T Period	7	21		
Severe AE, TT Phase, T Period	0	0		
Mild AE, TT Phase, M Period	104	93		
Moderate AE, TT Phase, M Period	55	64		
Severe AE, TT Phase, M Period	4	3		
Mild AE, Follow-up Phase	3	4		
Moderate AE, Follow-up Phase	3	3		
Severe AE, Follow-up Phase	0	0		

Notes:

[55] - ITT Population

[56] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants withdrawn due to AEs

End point title	Number of participants withdrawn due to AEs

End point description:

An AE is defined as any untoward medical occurrence in a participant temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product. An SAE is defined as any untoward medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, a congenital anomaly/birth defect, important medical events that jeopardize the participants or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

End point type	Secondary

End point timeframe:

Up to Week 50

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[57]	65[58]		
Units: Participants	0	7		

Notes:

[57] - ITT Population

[58] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants within each category of the Columbia Suicide Severity Rating Scale

End point title	Number of participants within each category of the Columbia Suicide Severity Rating Scale

End point description:

Prospective assessment of suicidality was conducted using an Interactive Voice Response System delivery of Columbia-Suicide Severity Rating Scale (eC-SSRS), a brief questionnaire designed to assess severity and change in suicidality by integrating both behavior and ideation using a validated interview algorithm. The result is a score from 1-9 for eC-SSRS based on increasing order of severity with 1-5 identifying suicidal ideation and 6-9 identifying suicidal behaviors. Data is presented for number of participants with any non-zero score for an ideation or a behaviour.

End point type	Secondary

End point timeframe:

Up to Week 50

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[59]	65[60]		
Units: Participants	2	2		

Notes:

[59] - ITT Population

[60] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the albumin and total protein values

End point title	Maximum on-treatment change from Baseline in the albumin and total protein values

End point description:

Albumin and total protein values were assessed at Baseline and Week 1, 2, 3, 4, 8, 12, 16, 20, 24, 28,

32, 36, 40, 44, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last pre-treatment value observed Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[61]	65[62]		
Units: Grams per liter				
arithmetic mean (standard deviation)				
Albumin	1.62 (± 2.272)	1.97 (± 1.904)		
Total Protein	3.697 (± 3.4905)	3.523 (± 3.143)		

Notes:

[61] - ITT Population

[62] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the alkaline phosphatase, alanine amino transferase, aspartate amino transferase and gamma glutamyl transferase values

End point title	Maximum on-treatment change from Baseline in the alkaline phosphatase, alanine amino transferase, aspartate amino transferase and gamma glutamyl transferase values

End point description:

Alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartate amino transferase (AST) and gamma glutamyl transferase (GGT) values were assessed at Baseline and Week 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last pre-treatment value observed Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[63]	65[64]		
Units: International units per liter				
arithmetic mean (standard deviation)				
ALP	11.17 (± 10.768)	9.69 (± 7.786)		
ALT	11.288 (± 14.1256)	20.954 (± 100.7119)		

AST	7.47 (± 8.0081)	10.738 (± 43.5443)		
GGT	8.091 (± 9.0464)	8.062 (± 16.4144)		

Notes:

[63] - ITT Population

[64] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the calcium, glucose, potassium, sodium and Urea/BUN values

End point title	Maximum on-treatment change from Baseline in the calcium, glucose, potassium, sodium and Urea/BUN values

End point description:

Calcium, glucose, potassium, sodium and Urea/BUN values were assessed at Baseline and Week 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last pre-treatment value observed Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[65]	65[66]		
Units: Millimoles per liter				
arithmetic mean (standard deviation)				
Calcium	0.083 (± 0.0744)	0.085 (± 0.0678)		
Glucose	1.221 (± 1.9247)	1.097 (± 0.8714)		
Potassium	0.486 (± 0.3658)	0.611 (± 0.495)		
Sodium	1.712 (± 1.5958)	1.831 (± 1.6637)		
Urea/BUN	1.356 (± 0.8213)	1.263 (± 1.1863)		

Notes:

[65] - ITT Population

[66] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the creatinine, direct and total bilirubin values

End point title	Maximum on-treatment change from Baseline in the creatinine, direct and total bilirubin values

End point description:

Creatinine, direct and total bilirubin values were assessed at Baseline and Week 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last pre-treatment value observed Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[67]	65[68]		
Units: Micromoles per liter				
arithmetic mean (standard deviation)				
Creatinine	8.47 (± 9.2012)	6.746 (± 6.6014)		
Direct Bilirubin	0.8 (± 0.789)	1.12 (± 0.927)		
Total Bilirubin	3.121 (± 3.4575)	3.923 (± 3.2128)		

Notes:

[67] - ITT Population

[68] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the creatinine clearance values

End point title	Maximum on-treatment change from Baseline in the creatinine clearance values

End point description:

Creatinine clearance values were assessed at Baseline and Week 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last pre-treatment value observed Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[69]	65[70]		
Units: Milliliter per minute (mL/min)				
arithmetic mean (standard deviation)	15.52 (± 11.067)	17.2 (± 12.946)		

Notes:

[69] - ITT Population

[70] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the basophils, eosinophils, lymphocytes, monocytes, platelets, total neutrophils and WBC count

End point title	Maximum on-treatment change from Baseline in the basophils, eosinophils, lymphocytes, monocytes, platelets, total neutrophils and WBC count

End point description:

Basophils, eosinophils, lymphocytes, monocytes, platelets, total neutrophils and white blood cell (WBC) count were assessed at Baseline and Week 1, 2, 3, 4, 8, 16, 24, 32, 36, 40, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last pre-treatment value observed Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[71]	65[72]		
Units: Giga cells per liter				
arithmetic mean (standard deviation)				
Basophils	0.0151 (± 0.0135)	0.0236 (± 0.02719)		
Eosinophils	0.111 (± 0.1023)	0.148 (± 0.213)		
Lymphocytes	0.7115 (± 0.67703)	0.7117 (± 0.60433)		
Monocytes	0.198 (± 0.1311)	0.188 (± 0.2071)		
Platelets	40.5 (± 29.258)	40.55 (± 26.041)		
Total Neutrophils	1.705 (± 1.6682)	1.751 (± 1.6871)		
WBC	1.902 (± 1.7481)	2.092 (± 1.7277)		

Notes:

[71] - ITT Population

[72] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the RBC and reticulocytes count

End point title	Maximum on-treatment change from Baseline in the RBC and reticulocytes count

End point description:

Red blood cell (RBC) and reticulocyte count were assessed at Baseline and Week 1, 2, 3, 4, 8, 16, 24, 32, 36, 40, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last Pre-treatment value observed Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[73]	65[74]		
Units: Trillion per liter				
arithmetic mean (standard deviation)				
RBC	0.261 (± 0.294)	0.289 (± 0.3327)		
Reticulocytes	0.0298 (± 0.02218)	0.038 (± 0.02987)		

Notes:

[73] - ITT Population

[74] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the hemoglobin and MCHC value

End point title	Maximum on-treatment change from Baseline in the hemoglobin and MCHC value

End point description:

Hemoglobin and mean corpuscular hemoglobin concentration (EMCHC) values were assessed at Baseline and Week 1, 2, 3, 4, 8, 16, 24, 32, 36, 40, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last Pre-treatment value observed Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[75]	65[76]		
Units: Grams per liter				
arithmetic mean (standard deviation)				
Hemoglobin	7.652 (± 7.8828)	7.769 (± 8.9246)		
MCHC	12.379 (± 5.8224)	11.6 (± 6.0255)		

Notes:

[75] - ITT Population

[76] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the MCH value

End point title	Maximum on-treatment change from Baseline in the MCH value

End point description:

Mean corpuscular hemoglobin (MCH) values were assessed at Baseline and Week 1, 2, 3, 4, 8, 16, 24, 32, 36, 40, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last pre-treatment value observed Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[77]	65[78]		
Units: Picograms				
arithmetic mean (standard deviation)	0.636 (± 0.6757)	0.448 (± 0.4341)		

Notes:

[77] - ITT Population

[78] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the MCV value

End point title	Maximum on-treatment change from Baseline in the MCV value

End point description:

Mean corpuscular volume (MCV) values were assessed at Baseline and Week 1, 2, 3, 4, 8, 16, 24, 32, 36, 40, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last pre-treatment value observed Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[79]	65[80]		
Units: Femtoliters				
arithmetic mean (standard deviation)	1.242 (± 1.8319)	1.169 (± 1.4745)		

Notes:

[79] - ITT Population

[80] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the hematocrit value

End point title	Maximum on-treatment change from Baseline in the hematocrit value

End point description:

Hematocrit values were assessed at Baseline and Week 1, 2, 3, 4, 8, 16, 24, 32, 36, 40, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last pre-treatment value observed Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[81]	65[82]		
Units: Fraction of 1				
arithmetic mean (standard deviation)	0.0191 (± 0.02445)	0.0228 (± 0.03024)		

Notes:

[81] - ITT Population

[82] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Urinalysis parameters at the indicated time points up to Week 50

End point title	Urinalysis parameters at the indicated time points up to Week 50

End point description:

Urine samples were collected, tested and monitored at Baseline and Week 1, 2, 3, 4, 8, 16, 24, 32, 36,

40, 48 and 50. Baseline value was defined as the last pre-treatment value observed. The data were monitored for safety throughout the conduct of the study and no summary analysis or change from baseline was conducted. The urinalysis assessments were: Appearance/clarity, Color, pH, Specific Gravity. Urine was checked for presence of the following by dipstick: bilirubin, occult blood, glucose, ketones, nitrite, protein and a marker for white blood cells. Data are available only at the participant level for each assessment performed.

End point type	Secondary

End point timeframe:

From Baseline up to Week 50

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[83]	0[84]		
Units: dipstick				
arithmetic mean (standard deviation)	()	()		

Notes:

[83] - ITT Population

[84] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with chemistry laboratory values outside the clinical concern range at any time on-treatment

End point title	Number of participants with chemistry laboratory values outside the clinical concern range at any time on-treatment

End point description:

Clinical chemistry parameters of potential clinical concern were assessed at Baseline and at Week 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. Any time on-treatment value was derived including values at scheduled and unscheduled assessments. Clinical chemistry parameters included ALP, ALT, AST, GGT, albumin, total protein, calcium, glucose, potassium, sodium, Urea/BUN, creatinine, direct bilirubin, total bilirubin and creatinine clearance. Number of participants with values in high and low categories based on deviation in parameter values from normal range are summarized.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[85]	65[86]		
Units: Participants				
ALT, High	0	1		
Albumin, High	0	0		
Albumin, Low	0	0		
ALP, High	0	0		
AST, High	0	1		
Calcium, High	1	1		
Calcium, Low	0	1		

Creatinine, High	0	0		
Direct Bilirubin, High	0	0		
GGT, high	0	1		
Glucose, High	2	0		
Glucose, Low	0	0		
Potassium, High	0	4		
Potassium, Low	0	0		
Sodium, High	0	0		
Sodium, Low	0	1		
Total Bilirubin, High	0	0		
Total Protein, High	0	0		
Total Protein, Low	0	0		
Urea/Bun, High	0	0		
Urea/Bun, Low	2	1		

Notes:

[85] - ITT Population

[86] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with hematology laboratory values outside the clinical concern range at any time on-treatment

End point title	Number of participants with hematology laboratory values outside the clinical concern range at any time on-treatment

End point description:

Clinical hematology parameters of potential clinical concern were assessed at Baseline and Week 1, 2, 3, 4, 8, 16, 24, 32, 40, and 48. The any time on-treatment value was derived including values at scheduled and unscheduled assessments.Clinical hematology parameters included basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, MCH, MCHC, MCV, monocytes, platelets, RBC, reticulocytes, total neutrophils and WBC. Number of participants with values in high and low categories based on deviation in parameter values from normal range are summarized.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[87]	65[88]		
Units: Participants				
Basophils, High	0	0		
Eosinophils, High	0	1		
Hematocrit, High	0	1		
Hematocrit, Low	1	0		
Hemoglobin, High	0	1		
Hemoglobin, Low	4	1		
Lymphocytes, High	1	0		
Lymphocytes, Low	2	0		
MCH, High	0	0		
MCH, Low	0	0		

MCHC, High	0	0		
MCHC, Low	0	0		
MCV, High	0	0		
MCV, Low	0	0		
Monocytes, High	0	0		
Platelets, High	0	0		
Platelets, Low	1	2		
RBC, High	0	1		
RBC, Low	0	0		
Reticulocytes, High	11	14		
Reticulocytes, Low	24	10		
Total Neutrophils, Low	5	6		
WBC, High	2	2		
WBC, Low	2	2		

Notes:

[87] - ITT Population

[88] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the systolic blood pressure and diastolic blood pressure

End point title	Maximum on-treatment change from Baseline in the systolic blood pressure and diastolic blood pressure

End point description:

Systolic blood pressure (BP) and diastolic BP were assessed at Baseline and at Week 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last Pre-treatment value observed. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[89]	65[90]		
Units: Millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Systolic BP	11.35 (± 9.547)	10.4 (± 9.818)		
Diastolic BP	10.21 (± 7.189)	8.49 (± 6.255)		

Notes:

[89] - ITT Population

[90] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the heart rate

End point title	Maximum on-treatment change from Baseline in the heart rate

End point description:

Heart rate was assessed at Baseline and Week 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last pre-treatment value observed. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[91]	65[92]		
Units: Beats per minute				
arithmetic mean (standard deviation)	10.41 (± 9.212)	11.05 (± 8.038)		

Notes:

[91] - ITT Population

[92] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the weight

End point title	Maximum on-treatment change from Baseline in the weight

End point description:

Weight was assessed at Baseline and Week 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last pre-treatment value observed. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[93]	65[94]		
Units: Kilograms				
arithmetic mean (standard deviation)	2.24 (± 2.088)	3.27 (± 2.738)		

Notes:

[93] - ITT Population

[94] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the heart rate as a measure of ECG assessment

End point title	Maximum on-treatment change from Baseline in the heart rate as a measure of ECG assessment

End point description:

Heart rate as a measure of electrocardiogram (ECG) assessment was assessed at Baseline and Week 2, 4, 12, 24, 36, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last pre-treatment value observed. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[95]	65[96]		
Units: Beats per minute				
arithmetic mean (standard deviation)	10.5 (± 9.57)	9.9 (± 8.65)		

Notes:

[95] - ITT Population

[96] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum on-treatment change from Baseline in the PR Interval, QRS duration, QT interval, QTcB, QTcF and RR Interval as a measure of the ECG assessment

End point title	Maximum on-treatment change from Baseline in the PR Interval, QRS duration, QT interval, QTcB, QTcF and RR Interval as a measure of the ECG assessment

End point description:

PR Interval, QRS duration, QT interval, QTcB, QTcF and RR interval as a measure of electrocardiogram (ECG) assessment were assessed at Baseline and Week 2, 4, 12, 24, 36, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. Baseline value was defined as the last pre-treatment value observed. Change from Baseline was calculated as the post-Baseline value minus the Baseline value.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[97]	65[98]		
Units: Milliseconds				
arithmetic mean (standard deviation)				
PR Interval	12.7 (± 12.03)	8 (± 10.36)		
QRS Duration	6 (± 6.7)	6.1 (± 6.45)		
QT Interval	12.8 (± 19.61)	16.4 (± 22.31)		
QTcB	15.8 (± 17.2)	16.5 (± 14.21)		
QTcF	10.8 (± 12.91)	12.1 (± 12.78)		
RR Interval	70.9 (± 116.57)	86.1 (± 112.05)		

Notes:

[97] - ITT Population

[98] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with change in the indicated vital sign with respect to the reference range and Baseline value

End point title	Number of participants with change in the indicated vital sign with respect to the reference range and Baseline value

End point description:

Vital sign parameters were assessed at Baseline and Week 1, 2, 3, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44 and 48. Any time on-treatment value was derived including values at scheduled and unscheduled assessments. Vital signs included systolic BP, diastolic BP, heart rate and weight. Vital signs are presented as: systolic BP: <90 or >140 and increase or decrease from Baseline >=30; diastolic BP: <50 or >90 and increase or decrease from Baseline >=20; Weight: Increase or decrease from Baseline >=7%; heart Rate: <50 or >100 and increase or decrease from Baseline >=30. Change from Baseline was calculated as the individual post-Baseline value minus the Baseline value. Baseline value is defined as the last pre-treatment value observed.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[99]	65[100]		
Units: Participants				
Systolic BP, <90 or >140, increase from BL >=30	1	2		
Systolic BP, <90 or >140, decrease from BL >=30	0	0		
Diastolic BP, <50 or >90, increase from BL >=20	2	0		
Diastolic BP, <50 or >90, decrease from BL >=20	0	0		
Weight, Increase from Baseline >=7%	7	9		
Weight, Decrease from Baseline >=7%	3	3		
Heart Rate, <50 or >100, increase from BL >=30	2	0		

Heart Rate, <50 or >100, decrease from BL >=30	0	0		

Notes:

[99] - ITT Population

[100] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with indicated change from Baseline in the indicated potential clinical concern ECG values

End point title	Number of participants with indicated change from Baseline in the indicated potential clinical concern ECG values

End point description:

ECG values were assessed at Baseline and Week 2, 4, 12, 24, 36, and 48. Maximum on-treatment value was derived including values at scheduled and unscheduled assessments. ECG parameters included QTcB and QTcF. ECG values are presented as: 0 - <=30 increase; >30 - <=60 increase and >60 increase from BL. Change from Baseline was calculated as the individual post-Baseline value minus the Baseline value. Baseline value is defined as the last Pre-treatment value observed.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Placebo QD	GSK239512 QD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[101]	65[102]		
Units: Participants				
QTcB, 0 - <=30 increase	44	48		
QTcB, >30 - <=60 increase	8	10		
QTcB, >60 increase	2	0		
QTcF, 0 - <=30 increase	50	47		
QTcF, >30 - <=60 increase	5	6		
QTcF, >60 increase	0	0		

Notes:

[101] - ITT Population

[102] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean GSK2586184 trough plasma concentrations at Weeks 4, 8, 24, 36 and 48

End point title	Mean GSK2586184 trough plasma concentrations at Weeks 4, 8, 24, 36 and 48[103]

End point description:

Trough pharmacokinetic (PK) samples were collected for all participants at Weeks 4, 8, 24, 36 and 48 prior to the daily dose (20 microgram (µg), 40 µg and 80 µg) of GSK239512. PK Population comprised of all participants for whom a pharmacokinetic sample was obtained and analyzed. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category

titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the PK Population.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 24, 36 and 48

Notes:

[103] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint only applies to the GSK2586184 arm.

End point values	GSK239512 QD			
Subject group type	Reporting group			
Number of subjects analysed	65[104]			
Units: Picograms per milliliter				
arithmetic mean (standard deviation)				
Week 4, 20 ug, n=4	18.228 (± 3.3496)			
Week 4, 40 ug, n=11	40.775 (± 20.0529)			
Week 4, 80 ug, n=48	80.641 (± 49.0002)			
Week 8, 20 ug, n=4	15.21 (± 3.5531)			
Week 8, 40 ug, n=6	30.753 (± 12.4895)			
Week 8, 80 ug, n=52	77.653 (± 41.9646)			
Week 24, 20 ug, n=3	13.627 (± 2.2262)			
Week 24, 40 ug, n=8	40.851 (± 20.0234)			
Week 24, 80 ug, n=44	84.8 (± 54.3398)			
Week 36, 20 ug, n=3	16.783 (± 6.4595)			
Week 36, 40 ug, n=6	39.082 (± 11.4493)			
Week 36, 80 ug, n=43	75.325 (± 62.746)			
Week 48, 20 ug, n=3	20.553 (± 7.225)			
Week 48, 40 ug, n=4	43.948 (± 24.5033)			
Week 48, 80 ug, n=36	93.909 (± 77.0032)			

Notes:

[104] - PK Population

Statistical analyses

No statistical analyses for this end point

Secondary: Mean GSK2586184 plasma concentrations at Weeks 8

End point title	Mean GSK2586184 plasma concentrations at Weeks 8[105]

End point description:

Pharmacokinetic (PK) samples were collected for all participants on Weeks 8 at pre dose, 0.5 hour (H), 2

H and 6 H post dose (20 µg, 40 µg and 80 µg) of GSK239512. Only those participants available at the specified time points were analyzed (represented by n=X, X in the category titles). Different participants may have been analyzed at different time points, so the overall number of participants analyzed reflects everyone in the ITT Population.

End point type	Secondary

End point timeframe:

Week 8

Notes:

[105] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint only applies to the GSK2586184 arm.

End point values	GSK239512 QD			
Subject group type	Reporting group			
Number of subjects analysed	65[106]			
Units: Nanograms per milliliter				
arithmetic mean (standard deviation)				
Pre-Dose, 20 ug, n=4	15.21 (± 3.5531)			
Pre-Dose, 40 ug, n=6	30.753 (± 12.4895)			
Pre-Dose, 80 ug, n=52	77.653 (± 41.9646)			
0.5 H, 20 ug, n=4	18.445 (± 0.6193)			
0.5 H, 40 ug, n=8	38.63 (± 13.9641)			
0.5 H, 80 ug, n=49	85.177 (± 50.7385)			
2 H, 20 ug, n=4	51.95 (± 24.1757)			
2 H, 40 ug, n=8	141.891 (± 68.144)			
2 H, 80 ug, n=49	195.431 (± 115.1998)			
6 H, 20 ug, n=4	52.768 (± 17.5052)			
6 H, 40 ug, n=8	103.084 (± 18.7014)			
6 H, 80 ug, n=49	191.989 (± 91.8976)			

Notes:

[106] - PK Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious adverse events (AEs) were collected from the start of administration of the study drug until the follow-up contact (up to Week 50).

Adverse event reporting additional description:

SAEs and non-serious AEs were reported for members of the ITT population, comprised of all participants who were randomised to treatment, and received at least one dose of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	GSK239512 QD

Reporting group description:

Add text

Reporting group title	Placebo QD

Reporting group description:

ENTER TEXT

Serious adverse events	GSK239512 QD	Placebo QD	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 65 (3.08%)	1 / 66 (1.52%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Thymoma			
subjects affected / exposed	1 / 65 (1.54%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral papilloma			
subjects affected / exposed	1 / 65 (1.54%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			
subjects affected / exposed	0 / 65 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vascular disorders			
Thrombophlebitis			
subjects affected / exposed	1 / 65 (1.54%)	0 / 66 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 65 (0.00%)	1 / 66 (1.52%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	GSK239512 QD	Placebo QD	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 65 (61.54%)	35 / 66 (53.03%)	
Nervous system disorders			
Dizziness			
subjects affected / exposed	6 / 65 (9.23%)	3 / 66 (4.55%)	
occurrences (all)	6	3	
Headache			
subjects affected / exposed	16 / 65 (24.62%)	11 / 66 (16.67%)	
occurrences (all)	27	18	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 65 (1.54%)	4 / 66 (6.06%)	
occurrences (all)	1	5	
Pyrexia			
subjects affected / exposed	1 / 65 (1.54%)	4 / 66 (6.06%)	
occurrences (all)	1	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 65 (3.08%)	6 / 66 (9.09%)	
occurrences (all)	3	7	
Psychiatric disorders			

Insomnia			
subjects affected / exposed	22 / 65 (33.85%)	7 / 66 (10.61%)	
occurrences (all)	25	7	
Middle insomnia			
subjects affected / exposed	5 / 65 (7.69%)	1 / 66 (1.52%)	
occurrences (all)	5	1	
Nightmare			
subjects affected / exposed	5 / 65 (7.69%)	0 / 66 (0.00%)	
occurrences (all)	6	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 65 (0.00%)	4 / 66 (6.06%)	
occurrences (all)	0	4	
Neck pain			
subjects affected / exposed	3 / 65 (4.62%)	4 / 66 (6.06%)	
occurrences (all)	3	5	
Infections and infestations			
Influenza			
subjects affected / exposed	5 / 65 (7.69%)	4 / 66 (6.06%)	
occurrences (all)	6	7	
Nasopharyngitis			
subjects affected / exposed	11 / 65 (16.92%)	14 / 66 (21.21%)	
occurrences (all)	16	24	
Urinary tract infection			
subjects affected / exposed	5 / 65 (7.69%)	2 / 66 (3.03%)	
occurrences (all)	6	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported